

Genetics Research

Summary: This program investigates ethical issues related to the conduct of genetic research involving human subjects, including issues related to recruitment, informed consent, risk benefit assessment, and sharing results with subjects.

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Background: The central aspiration of the Human Genome Project is to generate knowledge that translates into improvements in human health. Achieving this goal will require further research about the relationship among genes, environment and the phenotypic expression of disease. Additional research will be needed to assess how interventions based on this knowledge affect health. The conduct of such research raises ethical issues related to the protection of the rights and welfare of research subjects.

Most of these issues raised are not unique to genetics. Yet, genetics provides a useful prism to focus many contemporary research ethics issues. The novelty of the technologies and large number of subjects and researchers involved bring these general issues into clear relief. The four specific issues that we have focused on include subject recruitment, informed consent, risk benefit assessment and returning results.

First, recruitment is an ethically sensitive topic because it involves issues related to privacy and voluntariness. Is it appropriate for a physician or a family member to give a researcher the name of potential research participant? Some claim that giving a name and contact information is an unacceptable breach of confidentiality, and the subsequent solicitation for research is an unacceptable invasion of privacy. This issue has received considerable attention in the

aftermath of the case at Virginia Commonwealth University where information about a third party was requested from a research subject. Little is known about the public's attitudes about these issues but they must be addressed because family studies play an essential role in genetics research. An approach to responding this question developed in relation to a recent study of the impact of colon cancer education on the screening behavior of relatives of colon cancer patients (Colon Cancer Risk Counseling Study). Recruitment for this study involved contacting colon cancer patients listed on a cancer registry and asking them for the names of their relatives. At the annual review of this study, the University of Hawaii IRB felt that it was not appropriate to ask patients for the names of their relative for the purpose of recruitment. To address this issue, we are surveying this population.

Also, recruitment for research can engender ethical conflict in study coordinators who recruit subjects. Study coordinators must balance their responsibilities to maximize enrollment with their responsibilities to the advocate for patient/subjects interests. While the "dual role" of the investigator, as both a clinician and researcher, has been the subject of much commentary, there has been limited attention to the dual role of the study coordinator as clinician and researcher. We have conducted focus group to assess this issue.

Second, we have examined to role and limitations of informed consent in genetics research. An interesting challenge for genetics research relates to role of informed consent in protecting participants from risks by alerting them to the risks. This role makes sense when the risks occur as part of the research, and can thus be avoided if the potential participant does not become involved in the study. However, in research that involves the collection of genetic information, the risks may be related to the subsequent misuse of the information rather than during the study itself. There are few data about whether subjects recall these risks of disclosure and thus attempt to minimize them. We surveyed a group of relatives of Alzheimer Disease (AD) patients who participated in genetic research was surveyed to assess their understanding of the research.

In addition, other limitations of informed consent can be illustrated by the case of *in utero* gene transfer research. This issue came to our attention through participation in the Gene Therapy Policy Conference sponsored by the Office of Biotechnology Activities at the NIH in 1999 that addressed the scientific and ethical issues related to such research. One of the main concerns about such research is the vulnerability of parents who are hoping for a clinical intervention to help their fetus. It is tempting to suggest that this problem be primarily addressed by improving the informed consent. However, the solution should involve a more focused deliberation about the benefits and risks of the research and the appropriateness of any parent to enroll.

Third, there has been much little empirical or conceptual research on how the benefits of research are understood by various parties. Some empirical

research, primarily in psychiatric and oncology research, suggests that subjects mistakenly view research as similar to clinical care, believing that its primary intention is to provide direct benefits to patients rather than generalizable knowledge. Gene transfer research provides an illustrative case study to empirically examine how benefits of research are understood because it combines several salient characteristics including 1) early phase research, 2) oncology research, and 3) complex technology. There are few data about how subjects, researchers, and IRBs understand the benefits of such research in the benefit/risk assessment. This project is collaboration with investigators at UNC and Vanderbilt who have an extramural grant from NHGRI to assess how the participants in gene transfer research understand benefits.

Finally, many of the risks of genetic research revolve around the potential misuse of the subjects' genetic information. One way to minimize risks is to not provide individual results back to subjects. However, the eventual clinical use of genetics will necessarily involve the provision of results. This raises questions about the timing and circumstances of the transition between not providing results and providing results to participants. Even if there were not a clear expectation by the researcher or subject to share research results, circumstances, such as unexpected clinical implications, could strain these expectations.

Our interest in the dilemma of how to manage unanticipated research findings originated in a consultation with the Bioethics Consultation Service at the Clinical Center. NHGRI investigators and their Swedish collaborators were conducting a study of gene expression profiles in patients with breast cancer. The study involved the analysis of residual clinical samples from patients with sporadic breast cancer, as well as subjects in a study of BRCA1 related cancer. Research on the sporadic samples was approved by the IRB without consent but predicated on the expectation that results would not be communicated to the patients. A problem arose when one sample from a patient with sporadic cancer had the molecular profile of a BRCA1 patient, and researchers felt obligated to share this information with here. It is important to articulate in a systematic way, when and how researchers should share research results, to avoid *ad hoc* solutions.

Objectives:

- 1) To assess the attitudes of researchers and participants about recruitment strategies for subjects and family members
- 2) To understand the role and limitations of informed consent for genetics research
- 3) To understand how the benefits of clinical gene transfer research are considered by IRBs, investigators, study coordinators, and subjects
- 4) To develop an analysis of when individual research results should be provided to subjects

Methodology:

Objective 1: Focus groups were conducted with study coordinators who are involved in recruiting subjects for research. We conducted seven vignette-based focus group interviews with forty-five study coordinators from three different work settings, 1) a federal clinical research center, 2) an academic medical center, and 3) private sector organizations. The reason for interviewing study coordinators in three different setting is related to the assumption that a study coordinator's role in balancing research and clinical priorities would be influenced by the institutional setting. This project did not explicitly focus on genetic research, and included study coordinators involved with genetics research, drug interventions, and behavioral interventions. This approach reflects our view that the ethical issues with genetics research are not fundamentally unique.

We are currently surveying 1400 individuals who were recruited for the Colon Cancer Risk Counseling Study. Our objective is to 1) describe their attitudes about the acceptability of recruitment strategies to participate in cancer related genetics research, 2) determine the relationship of attitudes about recruitment strategies to other "recruitment-relevant attitudes", including attitudes about trust, privacy, medical care, medical research, and family relationships; and 3) examine the association between attitudes about recruitment strategies with decisions to participate in the Colon Cancer Risk Counseling Study. The survey will be sent by mail.

Objective 2: Exploration of informed consent issues has included both conceptual and empirical studies. First, we have evaluated data collected as part of a larger study of subjects who were enrolled in research about Alzheimer Disease (AD). These subjects all had a family history of AD and had Apolipoprotein E testing done as part of the study. Results were not provided to subjects. As part of a follow-up assessment of their involvement in this research study, 130 participants were asked to recall if that they had genetic testing, whether they recalled if their sample might be used for future research, and whether release of research records could affect their insurance.

The related conceptual project has been on the specific issues related to informed consent to *in utero* gene transfer research. The ethical issues related to consent and risk assessment are compounded by the prenatal context itself, as well as the fact that the fetuses would have very serious illnesses for which current interventions are not ideal.

Objective 3: This empirical study about benefits in research involved phone interviews with the Principal Investigators, Study Coordinators and subjects involved in 40 gene transfer studies conducted between 1999 and 2001. Additionally, 43 IRB chairs who reviewed gene transfer research were interviewed, and 320 consent forms were analyzed. The main research questions explored participants' specific understanding about the benefits of such research,

and what extent they distinguished between research and clinical practice and between the role of the physician and researcher. The interviews have been completed and the transcripts are currently being coded. The consent form coding has also been completed.

Objective 4: This practical dilemma about whether to inform subject of research results led to a more detailed conceptual assessment of the features that should guide researchers when unexpected results, particularly in someone who had not even consented to the test, should be given back the results.

Results:

Objective 1: Analysis of the focus groups showed that study coordinators are often engaged with the ethically sensitive issues that arise during subject recruitment, retention, and informed consent. They constantly balance advocacy for the patient, the subject, and the study. Despite expected differences according to workplace, focus group participants across all settings identified each of the advocacies and the need to keep them in balance. Our results provide clear evidence that study coordinators are key moral agents in research activities. Study coordinators are integral to the protection of research subjects because of their central position.

Objective 2: Exploration of the issues related to *in utero* gene transfer research suggested that the context of this research could undermine expectant parents comprehension of the study's benefits and risks, as well as the voluntariness of their decision to participate. To compensate for this limitation, and using the pediatric research regulations as a guide, a greater emphasis should be placed on the benefit/harm assessment rather than only informed consent. The most favorable benefit/harm assessment would be for those diseases/patients without other viable alternatives. In these circumstances, more serious risks would be more tolerable, even with limited likelihood of benefit.

In the study of people involved genetics research related to AD, we found that only 19% recalled that their samples would undergo genetic testing; 16% recalled that samples might be used for future research; and 15% recalled that release of research records could affect their insurance status. The risks of genetics research are often influenced by what subjects disclose to others after their research participation has ended. These data suggest that the current informed consent process – developed prior to widespread genetics research – may not be sufficient to minimize the research risks that these individuals face. Efforts to improve long-term understanding could involve supplemental education of subjects after their participation has been completed.

Objective 3: The interviews with the subjects, principal investigators and study coordinators are still being analyzed. A preliminary analysis of the 43 IRB chairs explored the question of how IRBs consider benefits to the subjects and benefits to society in their deliberations. Of the 41 respondents who discussed

benefits to subjects, 9 used terms that clearly indicated direct medical benefit and 14 used terms that clearly indicated collateral benefits (such as the access to medical care). The rest used non-specified words that could imply either direct or collateral benefits. Thirteen chairs explicitly stated that benefits to subjects were the primary consideration in their assessment of benefit, while eight thought that benefits society were the main consideration. This suggests diversity and ambiguity in one of the fundamental tasks of IRBs, which indicates a need for further consideration of the appropriate approach to assessing benefits. While this study was conducted in the context of gene transfer research, the implications of this project extend beyond genetics.

Objective 4: In the analysis of this case about returning results, we concluded that the researcher should contact the subject's primary clinical provider, and allow the clinician to make the decision about disclosure on clinical grounds. This analysis recognizes the distinction between clinical relationships and research relationships. It clarifies that it is not the "genetic" nature of the laboratory study that was determinative for the decision to reestablish contact. For example, known risk factors for patients at increased risk for carrying a BRCA mutation include age of cancer diagnosis, family history, and to a lesser degree, pathologic findings. A physician would be justified in conveying a request for further testing based upon any one of these features, and perhaps now based upon cDNA expression results. On the other hand, the lack of personal relationship would make it less appropriate for a medical researcher to contact an unknown subject with any one of these features. In this case, the subject was contacted by the primary physician, was tested for BRCA and did not have mutation.

Future Directions

Our current empirical projects are still in the data collection/analysis phase, including the recruitment survey and the study of benefits in gene transfer research. We plan to build on the prior work and look in a more synthetic fashion at the ethical implications of specific research studies that are explicitly designed to improve health outcomes.

Genetic information can improve health outcomes by identifying people who are at increased risk of treatable future illness by aiding in the selection specific interventions that may be safer or more efficacious. This benefits and risks of such research are physical, like the bulk of clinical trials, rather than psychosocial, like much genetics research. This research represents the intersection of clinical trials research and genetics research, and the ethical considerations involve the issues mentioned earlier in this section. Anticipation of the issues of such clinical trials is particularly important for successful design and conduct of studies that use genomics information to improve health. Specific research topics include newborn screening, primary care interventions, involvement of adolescents in gene transfer research, and involvement of adolescents in behavioral genetics research.

Research on newborn screening is not novel but likely to increase. There are many proposals to expand newborn screening, and some proposals that such expansions should be preceded by research. We plan to look at the ethical issues that have arisen in prior newborn screening research, and consider the implications of these issues for future studies. These issues include approaches to informed consent, the use of control groups and withholding information, future use of samples, genetic counseling for carriers, and availabilities of treatments.

Another set of ethical questions related to studying the impact of genetic testing in a “natural primary care setting.” That is, a setting with truncated education, consent and counseling. Generally research studies, even in primary care, have robust approaches to these three practices, but once in clinical practice, there is less attention to these issues and limited data about the impact of the practices on patients. This project is motivated by the pilot study described in the pharmacogenomics and clinical applications program on the use and impact of genetic testing for colon cancer risk in the primary care setting.

Research related to behavior genetics raises unique challenges. We have recently initiated an evaluation of ethical issues in involving adolescents in genetics-based smoking intervention studies. This is an outgrowth of an NCI funded project at Georgetown/University of Pennsylvania on genetic influence on smoking related behavior. A related “ethics and policy project” has been funded by Robert Wood Johnson to look at the ethical implications of such research. We have been taking the lead considering the specific issues that would need to be considered in such trials. These issues include recruitment strategies, informed consent, and the communication of pleiotropic results.

The special challenges of enrolling adolescents in gene transfer research builds on our interests in both the gene transfer context and issues related to recruitment and consent. The idea for this project stems from work developing a program for “decision monitoring” for a phase I/II trial gene transfer study involving adolescents with cystic fibrosis. We plan to assess the impact of this program empirically by interviewing the investigators, decision monitors, adolescents and parents. We plan to conduct conceptual work on the appropriate role of “decision monitoring” based on articulating distinct goals of the process and relating these goals to specific practices.

Publications:

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